REMARKS

Objections to the Specification

The Final Office Action objected to the alleged presence of embedded hyperlinks in the text of the application on page 26. In response, the Applicants have deleted the objectionable text from the specification.

Claim Rejections – 35 U.S.C. § 112

The Final Office Action rejects claims 1 and 19 because they recite a method for improving the binding affinity of a ligand for a target and do not provide a step of improving the binding affinity. While the applicants do not believe that such a step is required in the claim, inasmuch as the step necessarily occurs when one carries out the recited sequence of steps, out of a spirit of cooperation and in order to have the application more promptly issued to allowance, applicants have amended claims 1 and 19 to indicate that the binding affinity of the first ligand for the biological target is improved by the process.

The Advisory Action continues to object to the use of the term "substantially" in the claims because it is allegedly indefinite. During the interview of February 15, 2005, the Examiner expressed her view that the term interjected ambiguity and that removal of the term would not affect the scope of the claims because it is implicitly recognized that one can never construct a composite ligand that matches exactly the distances and orientations of the ligands deduced in the method of the claims. Based on this understanding, and in a spirit of cooperation in order to have the application more promptly allowed, applicant has removed the term "substantially" from the claims.

Claim Rejections – 35 U.S.C. § 103

Johnson et al. (1999) is the reference focused on particularly during the interview. It is respectfully submitted that the proposed amendment overcomes the Johnson reference and any secondary references with which it could be combined.

On page 620, in column 2, Johnson describes a composite protein that he constructed from two cellulose binding domains (CBD_{N1} and CBD_{N2}) of the CenC beta-1,4-glucanase

enzyme. He reports that the affinity of the composite protein for amorphous cellulose is approximately twice as great as CBD_{N1} individually.

Johnson undertook the making of a composite protein by linking separate protein domains, not a composite ligand as described in the present invention. Johnson did not undertake any of the steps undertaken by the inventors of the present invention to arrive at his composite protein, and would not have motivated anyone to take the steps recited herein because he was not concerned with linking domains of a protein at a preferred orientation and distance to improve their binding affinity for a ligand. Johnson was studying the linker to gain some understanding of the binding characteristics of the CBDs to cellulose, but ultimately he concluded that the relative orientation of the protein domains did not even matter, because "the tandem CBDs anchor CenC to its natural substrate … without a strong preference for their orientations." (P. 720 at col. 2.)

Johnson was not concerned with constructing a composite ligand with improved affinity for a biological target, and never undertook any of the steps that the present inventors have identified for improving that affinity. In particular, Johnson never addressed the issue of a distance between a first and second ligand and never "determine[ed] whether a second ligand perturbs peaks on the second NMR spectra that are also perturbed by the paramagnetic label on the first NMR spectra," as required by clause (d) of claim 1. That step would only be performed if one was interested in determining whether the two ligands bound to the target molecule at an ascertainable distance, and constructing a composite ligand at the distance ascertained. Moreover, no orientational data from dipolar couplings were collected as described in claims 1e, 7, 19e and 20b. The "orientation" of the cellulose-derived ligand actually refers to a "direction" of binding in the protein site which proves to be ambiguous, as opposed to a three dimensional orientation. This latter information was also dependent on use of assigned protein resonances, a step not needed in the present invention.

The examiner also mentioned another new reference during the telephone conference of May 15 – US 5,989,827 to Fesik. This patent is specifically discussed in the background of the patent, wherein it is stated:

> A series of patents to Fesik et al., U.S. Patent Nos. 5,698,401; 5,804,391; 5,891,643; 5,989,827; and 6,043,024 ("the Fesik patents") disclose such efforts, through a technique known as "SAR by NMR."

SAR by NMR uses a very sensitive two dimensional NMR experiment, a heteronuclear single quantum coherence (HSQC) experiment, to screen compound libraries for components that bind to protein targets, and uses a mapping of perturbed peaks to points in a three dimensional protein structure from the HSQC experiment to locate sites of binding on a protein surface. The experiment relies on uniform ^{15}N enrichment of the protein target and collection of peaks that correlate the ^{1}H and ^{15}N chemical shifts of directly bonded ^{15}N-^{1}H pairs that occur primarily in backbone amide bonds of the protein, one pair per residue. Effects on the chemical shifts of peaks coming from amide pairs on binding of drug components is largely restricted to proximate residues, and thus provides qualitative information on the location of the binding site for any one component. If the peaks can be assigned to specific amino acids and if the protein structure is known, the binding site can be spatially localized. When more than one interacting component can be localized, components binding to proximal sites can be assembled synthetically to achieve binding affinities that approximate the product of the individual component affinities. Thus, compounds that individually fail as drug leads because of low binding affinities can be combined to produce viable leads.

The SAR approach, while successful, is limited. The procedure does require assignment of peaks to the amino acid sequence of the protein, and it does require knowledge of the three dimensional structure of the protein. It is also often the case that additional experiments involving nuclear Overhauser effects (NOEs) between protons on a binding component and protons on the protein are needed to restrict possible orientations of each binding component relative to the protein surface and better define the relative geometries of components to be linked synthetically. Thus, even though the basic HSQC screen experiment is highly efficient, the additional experiments needed for assignment and structure determination are very time consuming. They also begin to fail when proteins become large. Work to date has been restricted to proteins that are less than 40 kDa in molecular weight and soluble to levels approaching 0.5 mM.

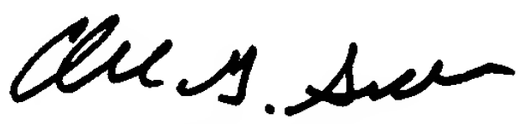
The Fesik patents would not have motivated a skilled worker to practice the method of the claimed invention because, once again, Fesik does not teach the step of "determining whether the second ligand perturbs peaks on the second NMR spectra that are also perturbed by the paramagnetic label on the first NMR spectra," as required by clause (d) of claim 1. Fesik was determining where on the backbone of a structurally characterized protein two ligands bound, by determining which peaks on the backbone of the protein were perturbed by the ligands. The present invention, in contrast, generally requires one to compare the peaks from the backbone of the protein that are perturbed by the first ligand and the second ligand and, if the first and second

ligands perturb the same peaks on the backbone, then one knows that they are binding to the protein in close proximity, and can be constructed into a composite ligand based on that proximity. It does not require assignment of peaks to specific amino acids in the protein sequence, and it does not require knowledge of a three dimensional protein structure. This is a new and nonobvious concept that is clearly set forth in the claims, and that clearly distinguished the claimed invention from the prior art.

CONCLUSION

Applicants trust that the foregoing amendment and explanation is adequate to place this application in condition for allowance, and welcome any further discussions or conversations that will facilitate the Examiner's consideration. Please grant any extension of time required to enter this response and charge any additional fee, or credit any overpayment to Deposit Account No. 11-0980.

Respectfully submitted,



Clark G. Sullivan
Reg. No. 36,942

March 22, 2005
KING & SPALDING LLP
191 Peachtree Street
Atlanta, GA 30303
(404) 572-4600 (Telephone)
(404) 572-5145 (Facsimile)
04342.105053